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ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING
GROUND MD MAR 86 USAEHA-75-51-0573-86

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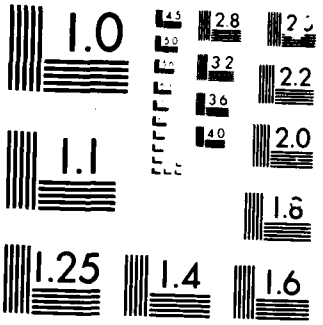

MICROCOPY RESOLUTION TEST CHART

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UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

ABERDEEN PROVING GROUND, MD 21010-5422

AEHA

TERATOLOGICAL ASSESSMENT OF TRINITRO - RDX IN RATS
STUDY NO. 75-51-0573-86
JUNE 1985 - JANUARY 1986

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19. ABSTRACT (Continue on reverse if necessary and identify by block number)

A teratology study in rats was performed to define the effects of trinitro - RDX on the developing fetus, oral dosage levels of 2, 6 and 20 mg rat/kg/day were administered to pregnant female rats critical period of organogenesis. Fetuses derived from RDX - treated dams had significantly lower body weights and lengths when compared to control fetuses. It was recommended that human females of childbearing age be protected from exposure to trinitro - RDX by means of appropriate industrial hygiene practices. It was further recommended that additional developmental toxicity studies be performed.

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO
ATTENTION OF

HSHB-OT

28 March 1986

SUBJECT: Teratological Assessment of Trinitro - RDX in Rats, Study No. 75-51-0573-86, June 1985 - January 1986

HQDA(DASG-PSP)
5111 Leesburg Pike
Falls Church, VA 22041-3258

EXECUTIVE SUMMARY

The purpose and a summary of the recommendations of the enclosed report follow:

a. Purpose. This study was designated to define the teratogenic potential, if any, of oral administration of trinitro-RDX in rats.

b. Recommendations.

(1) To ensure regulatory compliance, it is recommended that human females of childbearing age be protected from exposure to trinitro-RDX by means of appropriate industrial hygiene practices.

(2) To elucidate the developmental toxicity properties of trinitro-RDX, the following recommendations are made: A teratology study in a second species, the rabbit or ferret, should be conducted. Further, a two generation reproduction study in rats should be performed.

FOR THE COMMANDER:

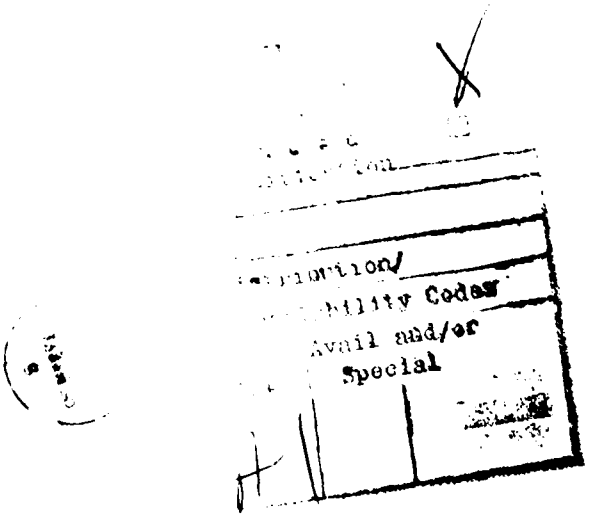
Encl

for N. JOE THOMPSON
Colonel, MC
Director, Occupational and Environmental Health

CF:
Cdr, HSC (HSCL-P) (w/encl)
Cdr, AMC (AMCSG-O) (w/encl)

Study No. 75-51-0573-86, Jun 85 - Jan 86

CONTENTS



DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO ATTENTION OF

HSHB-OT

TERATOLOGICAL ASSESSMENT OF TRINITRO-RDX IN RATS STUDY NO. 75-51-0573-86 JUNE 1985 - JANUARY 1986

1. AUTHORITY. Letter, HQ AMC, AMCSG-O, 25 February 1985, subject: Request for Trinitro - RDX Data.

2. REFERENCES. See Appendix A for a list of references.

3. PURPOSE. This study was designed to define the teratogenic potential, if any, of oral administration of trinitro-RDX in rats.

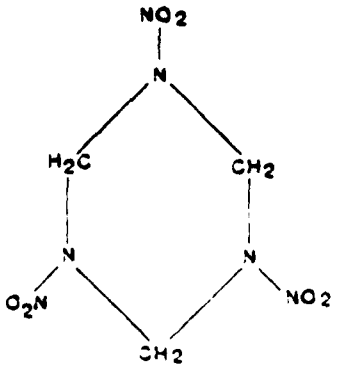
4. BACKGROUND.

a. Trintro-RDX (RDX: 1,3,5-Trinitro - 1,3,5-triazacyclohexane), a widely used military explosive, has been the subject of many studies to determine its toxicity. A review of the available literature and ongoing research revealed that only limited toxicity work had been done with RDX in the areas of developmental toxicology such as teratology and reproduction (reference 1).

b. The Toxicology Division, USAEHA, was tasked by the Office of The Surgeon General to perform needed teratology studies with trinitro-RDX. The results from these studies are to provide guidance to the US Army Materiel Command (AMC) pregnancy surveillance program (reference 2).

c. The laboratory rat was selected as the species of choice for this study which was conducted in accordance with guidelines set forth by the US Environmental Protection Agency (EPA) as per reference 3.

5. TEST MATERIAL. The trinitro-RDX used in this study was supplied by Holston Army Ammunition Plant, Kingsport, Tennessee. The purity was reported at 90 percent using liquid chromatography methodology. It is described as unsorted (not sieved) and has the appearance of fine white crystals containing some moisture. The chemical structure follows:



Trinitro-RDX is identified by CAS Registry Number 121-82-4. It has a molecular formula of $C_3H_6N_6O_6$ and a molecular weight of 222.15. Commonly used synonyms include cyclonite; cyclotrimethlenetrinitramine; hexagen; hexahydro-1,3,5-trinitro-s-trimzine; hexalite; RDX; T4; S-Triazine, hexahydro-1,3,5-trinitro; and 1,3,5-triazacyclohexane.

6. METHODS. The laboratory studies were divided into two subsets. A pilot study was first performed to establish acceptable dosage levels for the main teratology study. Compound analysis appears as Appendix M.

a. Pilot Study.

(1) Virgin female and naive male sexually mature, Sprague-Dawley rats, 9 to 12 weeks of age, were used to produce pregnancies. These rats were obtained from Charles River Breeding Laboratories and were identified as CRL:COBS-CD-(SD)BR colony animals.

(2) All rats were maintained in a temperature-, humidity- and light-controlled room. The conditions were 70° F ± 5°, 50 percent ± 5 percent and a 12-hour light, 12-hour dark cycle. A certified pesticide free rodent chow and water were available ad libitum (reference 4).

(3) A ratio of one male and two or three female rats housed together was used during the mating procedure. The occurrence of copulation was established by daily (morning) inspection for sperm plugs on the pad under the cage followed by a positive vaginal wash. A positive finding set day "0" of gestation. Thirty-six positively mated female rats were identified by toe clip, housed individually, and assigned among five treatment groups and one control group. Dosages of trinitro-RDX selected as fractions of a reported oral dose of 119 mg/kg were 120, 80, 40, 20 and 10 mg/kg/day. Single daily doses of the compound, suspended as 3 percent in 10 percent gum acacia, were administered by gavage beginning on day 6 of gestation and continued up to and including day 15 of gestation. The control group received the vehicle only, 4 mL/kg/day, on a comparable regimen. Individual daily oral doses were based on the animal's body weight on day 6 of gestation.

(4) All females were observed daily for changes in appearance and behavior. A gross necropsy was performed on all rats which died before the scheduled sacrifice day.

(5) All females were weighed on gestation days 0, 6, 10, 13, 16 and 20.

(6) On the morning of the 20th day of gestation, each female (dam) was sacrificed by CO_2 inhalation and the uterus and ovaries exposed by laporotomy. The number and location of viable fetuses, nonviable fetuses, resorptions, total implantations and corpora lutea were recorded. The dams were examined for gross pathological changes before being discarded. Fetuses were individually weighed, measured, sexed and examined for external malformations. Each fetus was then dissected and examined for visceral anomalies before being discarded. These fetal examinations were conducted to screen for potential fetal toxicity and/or teratogenicity.

(7) The lowest dosage level affecting maternal weight gain or producing other outward signs of maternal toxicity was chosen as the highest dosage level for the teratology study.

b. Teratology Study.

(1) Upon completion of the pilot study, 120 female and 48 male CRL:COBS-CD-(SD)BR rats were received at 7 weeks of age. After an acclimation period of several weeks, they were grouped for mating, checked for sperm, identified and housed as in the pilot study. The mating procedure continued until there were at least 25 positively mated females in each dosage group.

(2) Daily oral dosing commenced on day 6 of gestation and continued through day 15 of gestation. Daily dosages of RDX selected for this study were 2, 6 and 20 mg/kg/day. Trinitro-RDX was suspended as 0.5 percent in 10 percent aqueous gum acacia. Vehicle controls received 4 mL of 10 percent aqueous gum acacia/kg/day.

(3) All females were observed daily for physical and behavioral deviations. Animals were weighed on days 0, 6, 10, 13, 16 and 20 of gestation. Any rats found dead or moribund during the course of the study were submitted for gross necropsy.

(4) On the 20th day of gestation, each female (dam) was sacrificed by CO^2 inhalation. Each uterus was exposed and counts were made of corpora lutea, implantation sites, resorptions and fetuses. The gravid uterus was then excised and weighed. This weight was subtracted from the terminal female body weight in order to determine absolute body weight gain/loss during gestation. All fetuses were removed from the uterus, assigning each a number starting from upper the dam's right and proceeding to upper left. After measurements of weight and length (crown to rump), as well as gross observation and sexing, all fetuses were tagged for permanent identity. Odd-numbered fetuses were placed in denatured ethanol for skeletal preparation while even-numbered fetuses were placed in Bouin's fixative for soft tissue examination. A record of the above sacrifice procedures were recorded on HSE-LT Form 40, Prenatal Toxicity Record.

(5) Fetal examinations were conducted as per reference 5. Findings were recorded on either HSE-LT Form 53-1, Fetal Skeletal Examination or HSE-LT Form 53, Soft Tissue Examination.

(6) The Mann-Whitney "U" test and Student's "t" test were the statistical methods used to develop findings. Experimental data were collected on the specialized forms, large tabular sheets or in laboratory notebook number 108.

(7) The USAEHA Quality Assurance Office inspected each phase of this study to ensure that Standard Operating Procedures were adhered to.

7. RESULTS.

a. Pilot Study.

(1) All females receiving trinitro-RDX, 40 mg/kg/day, 80 mg/kg/day and 120 mg/kg/day died before the end of their dosing periods. Convulsions were observed preceeding death and a bloody discharge around mouths and noses was noted consistently at necropsy.

(2) Animals receiving trinitro-RDX, 20 mg/kg/day, displayed urogenital discharge and some red nasal discharge throughout the dosing period. Those receiving trinitro-RDX, 10 mg/kg/day, were asymptomatic.

(3) Pups derived from RDX-treated dams were externally normal, but had significantly lower body weights when compared with control pups.

b. Teratology Study.

(1) The following parameters were calculated from data derived from this teratology study (Appendix B):

$$\text{Fertility index:} \quad \frac{\text{pregnant animals}}{\text{positively mated animals}} \times 100$$

$$\text{Gestation index:} \quad \frac{\text{viable litters}}{\text{pregnant animals}} \times 100$$

$$\text{Index of alive fetuses:} \quad \frac{\text{alive fetuses}}{\text{total fetuses}} \times 100$$

$$\text{Resportion index:} \quad \frac{\text{total number of resorptions}}{\text{total number of implantations}} \times 100$$

$$\text{Index of variants:} \quad \frac{\text{total number of fetuses with variations}}{\text{total number of fetuses}} \times 100$$

$$\text{Index of malformations:} \quad \frac{\text{total number of fetuses with malformations}}{\text{total number of fetuses}} \times 100$$

Variants: Anomalies considered to be minor variations from the normal such as retarded ossification or slight hydronephrosis.

Malformations: Life threatening or debilitating defects such as exencephaly, gastroschisis or cleft palate.

Early resorption: Deciduoma or placental remains only.

Late resorption: Placental and embryonic remains.

Runt: A fetus weighing 70 percent or less than the mean weight of its litter.

(2) Maternal Parameters.

(a) One pregnant female from each of the groups receiving trinitro-RDX, 2 mg/kg/day and 6 mg/kg/day, died spontaneously during the test period. No overt signs were noted for these animals.

(b) Mortality was high among females receiving trinitro-RDX, 20 mg/kg/day, with 31 percent dying during the test period. Premortem signs included urogenital discharge, red nasal and oral exudate, convulsion and prostration. Gross necropsies did not reveal specific cause of death.

(c) Several surviving females at the 20 mg/kg/day dosage level displayed such signs as convulsions; nasal, oral, and urogenital discharge; alopecia and hyperactivity.

(d) For pregnant rats surviving to day 20 of gestation in the group receiving trinitro-RDX, 20 mg/kg/day, body weights were significantly lower than controls on days 10, 13 and 16 of gestation. Body weights for those dams were more comparable to control by day 20 of gestation (Appendices C-G).

(e) No significant changes were noted in dams of any group at time of necropsy on day 20 of gestation.

(f) Surviving females at time of necropsy had comparable fertility and gestation indices (Appendix B). One dam in the trinitro-RDX, 20 mg/kg/day group was found to be impregnated, but had no viable fetuses. The fertility index for controls and RDX, 2mg/kg/day, was 64 percent while that index for RDX, 6 mg/kg/day, and RDX, 20 mg/kg/day,, was 74 percent. The gestation index was 100 percent in all groups except that receiving RDX, 20 mg/kg/day, where the gestation index was 94 percent.

(g) Preimplantation loss (corpora lutea-minus implantations) was not a factor in this study. Implantation had taken place before treatment was begun.

(3) Fetal Parameters (Appendices B and H-K).

(a) There were no statistically significant differences in implantations per dam or fetuses per dam when treatment groups were compared with controls.

(b) A trend toward increase was found in resorptions (in utero deaths) per dam. This increase was not dose related, but all treatment groups showed a higher incidence of resorption (6 percent each) than controls (5 percent). One fully developed fetus was not viable at time of necropsy in the 2 mg/kg/day group.

(c) The weights and lengths of fetuses (pups) in all trinitro-RDX treated groups were found to be significantly reduced from those of control pups. The reduction was generally dose-related.

(d) A shift in sex ratio toward male predominance was observed with an increase in trinitro-RDX dosage.

(e) Although the species used in this study has been shown to be susceptible to chemically-induced terata in this laboratory, no teratological findings of biological relevance were noted among controls or trinitro-RDX treated litters.

(4) Quality Assurance. The quality assurance performed for this study is summarized in Appendix L.

8. DISCUSSION.

a. The occurrence of major malformations in an initial screening test for teratogenicity such as this cannot always be depended upon to indicate an embryopathic effect. Frank malformations (terata) are usually a factor of a balance of dosage and timing. Because of this, more reliable indicators of embryopathic activity such as increased embryonic death or decreased fetal weight should be considered when evaluating the results of a teratology test (reference 6).

b. In this study, Trinitro-RDX produced slightly, yet significantly, lower mean fetal body weight and length when treated groups were compared to the control group. This finding was dose-related. Although there was no dose-related increase in malformations or variations in pups derived from RDX-treated dams, the above would indicate some potential for embryopathic activity.

c. Methyl parathion has been shown to cause lower fetal weights in rats, while producing major malformations in mice (reference 7). This and other studies (i.e. thalidomide) make it prudent to perform a teratology study in a second species. Multigeneration reproduction studies are also desirable when evaluating postpartum implications of developmental toxicity.

d. The current TLV/TWA for Trinitro-RDX is 1.5 mg/m_3 (skin). RDX may enter the body by oral, dermal and/or inhalation routes. The compound was shown in this study to be developmentally toxic at a dosage of 2mg/kg/day. This level of exposure may certainly be expected in areas where good industrial hygiene practices are not employed.

9. CONCLUSIONS.

a. Trinitro-RDX at a dosage as low as 2 mg/kg/day, orally, has been shown to cause reduced fetal size in pups derived from maternal rats receiving that compound during the major period of organogenesis. Under the conditions of this study, RDX is considered to be developmentally toxic (embryopathic).

b. The toxic effects of trinitro-RDX are cumulative in adult female rats. Multiple daily doses of the compound at sub-lethal levels produce increasingly severe effects, including death.

c. No "No Effect Level" for embryopathic activity can be established by this study.

10. RECOMMENDATIONS.

a. To ensure regulatory compliance, it is recommended that human females of childbearing age be protected from exposure to trinitro-RDX by means of appropriate industrial hygiene practices (AR 40-5, paragraph 5-16).

b. The following recommendations are made to elucidate the developmental toxicity properties of RDX:

(1) A teratology study in a second species, the rabbit or ferret, should be conducted.

(2) A two generation reproduction study in rats should be performed to assess developmental effects of trinitro-RDX.

RICHARD A. ANGERHOFER
Biologist
Toxicology Division

GURVIS DAVIS
Biological Lab Technician
Toxicology Division

LYNN BALCZEWSKI
SP4
Animal Care Specialist
Toxicology Division

APPROVED:

MAURICE H. WEEKS
Chief, Toxicology Division

APPENDIX A

REFERENCES

1. Letter, USAEHA, HSHB-OT, 22 April 1985, subject: Request for Trinitroso-RDX Data.

2. AR 40-5, 1 June 1985, Preventive Medicine.

3. United States Environmental Protection Agency Publication No. EPA 560/G-82-001, Health Effect Test Guidelines, 1982.

4. Standing Operating Procedure, USAEHA, HSHB-OT/WP, US Army Environmental Hygiene Agency, March 1982, subject: Animal Facilities, Toxicology Division, Buildings E-2100 and E-2101.

5. Toxicology Division Standing Operating Procedures, US Army Environmental Hygiene Agency (USAEHA), 1980-1985.

6. Standing Operating Procedures, USAEHA, HSHB-OT, April 1985, subject: Teratology Study in Rats.

7. A.K. Palmer, "The Design of Subprimate Animal Studies," Handbook of Teratology, Vol IV, Chapter 8, p 215-265 (1977).

8. T. Tanimura, et al, "Embryotoxicity of Acute Exposure to Methyl Parathion in Rats and Mice," Arch. Environmental Health, 15:609-613 (1967).

APPENDIX B

SUMMARY OF MATERNAL AND FETAL PARAMETERS

Parameter	Control (10 Gum Acacia)	RDX 2 mg/kg/day	RDX 6 mg/kg/day	RDX 20 mg/kg/day
Females mated	39	40	40	51
Fatalities	0	1	1	16
Females at Sacrifice	39	39	39	35
Females Pregnant	25	25	29	26
Fertility Index (%)	64	64	74	74
Litters	25	25	29	25
Gestation Index (%)	100	100	100	96
Implantations, Total	352	363	391	373
Implantations, per Dam	14.1	14.5	13.5	14.4
Fetuses, Total	335	341	368	349
Fetuses per Dam	13.4	13.6	12.7	13.4
Index of alive fetuses (%)	100	100	100	100
Dead Fetuses, Total	0	1	0	0
Dead Fetuses per Dam	0	0.04	0	0
Resorptions, Total	17	22	23	24
Early Resorptions	17	22	23	23
Late Resorptions	0	0	0	1
Resorptions per Dam	0.68	0.88	0.79	0.92
Resorption Index	5	6	6	6
Variants, Total	23	22	25	31
Variants per Dam	0.92	0.88	0.86	1.19
Index of Variants (%)	7	6	7	9
Malformations, Total	1	1	0	2
Malformations per Dam	0.04	0.04	0.00	0.08
Index of Malformations (%)	0.3	0.3	0.0	0.6
Runts	0	0	0	0
Average Fetal Weight (gm)	3.78	3.63*	3.70*	3.45*
± Standard Deviation	0.51	0.33	0.37	0.46
Average Fetal Length (cm)	3.69	3.64*	3.66*	3.52*
± Standard Deviation	0.22	0.18	0.20	0.25
Sex Ratio (M/F)	.83	.88	.94	.99

* Statistically significant at the 0.05 level of probability

Study No. 75-51-0573-86, Jun 85 - Jan 86

APPENDIX C
SUMMARY OF MATERNAL BODY WEIGHTS - GRAMS
(Pregnant rats only)

Dosage Group		Day 0 Mated	Day 6	Day 10 Treatment	Day 13	Day 16 Post-treatment	Day 20	Day 20 Adjusted
				Day of Gestation				
Gum Acacia Control 4mL/kg/day	x	228	249	256	269	289	348	269
	±SD	16	18	18	18	18	26	19
Trinitro-RDX 2 mg/kg/day	x	234	253	263	277	299	356	278
	±SD	20	23	21	23	26	35	25
	t	1.20	0.64	1.31	1.45	1.46	1.02	1.45
	DF	48	48	48	48	48	48	48
Trinitro-RDX 6 mg/kg/day	x	227	247	251	265	284	340	266
	±SD	22	22	23	24	28	37	25
	t	0.07	0.40	0.76	0.64	0.76	0.87	0.48
	DF	52	52	52	52	52	52	52
Trinitro-RDX 20 mg/kg/day	x	232	247	234*	250*	270*	335	259
	±SD	20	24	21	27	26	37	24
	t	0.76	0.30	3.86	2.95	3.08	1.41	1.57
	DF	48	48	48	48	48	48	48

* Significantly lower than controls at the 0.05 level of probability

APPENDIX D

INDIVIDUAL MATERNAL BODY WEIGHTS-GRAMS
(Pregnant Rats Only)
GUM ACACIA CONTROL
4 mg/kg/day

Dam Number	Day 0 Mated	Day 6 Treatment Starts	Day 10	Day 13	Day 16 Post-Treatment	Day 20 Sacrifice	Day 20 Adjusted
			Day of Gestation				
1418	225	257	257	277	276	322	277
1419	210	224	228	248	255	286	253
1422	205	243	235	267	284	338	265
1426	210	240	248	265	276	331	256
1428	244	266	279	295	309	271	292
1430	246	270	285	295	314	376	289
1434	229	236	248	261	268	307	261
1435	207	230	246	259	275	330	250
1436	219	241	254	236	280	341	260
1439	253	279	278	289	290	357	284
1441	195	211	217	227	260	315	209
1521	219	254	260	281	309	374	281
1601	234	262	276	282	311	377	292
1605	240	246	254	266	288	352	262
1609	227	249	249	263	284	352	261
1613	267	291	294	303	323	389	300
1617	236	270	275	288	316	378	287
1621	240	259	265	275	299	366	266
1625	224	248	259	262	291	349	266
1629	235	255	262	280	312	374	290
1633	233	243	243	262	281	337	268
1637	219	236	239	251	270	319	254
1641	235	243	251	267	276	358	268
1645	225	244	249	266	285	348	275
1649	213	234	241	256	277	345	261

APPENDIX E

INDIVIDUAL MATERNAL BODY WEIGHTS-GRAMS
(Pregnant Rats Only)
TRINITRO-RDX
2 mg/kg/day

Dam Number	Day 0 Mated	Day 6 Treatment Starts	Day of Gestation Day 10	Day 13	Day 16 Post-Treatment	Day 20 Sacrifice	Day 20 Adjusted
1444	237	266	274	393	329	404	309
1446	214	224	247	245	268	324	239
1454	230	250	255	268	282	338	269
1459	219	230	249	255	275	328	255
1460	207	223	231	249	260	280	249
1461	213	231	248	258	284	331	250
1463	248	268	288	283	319	368	282
1464	261	275	284	308	328	388	296
1465	287	309	304	327	358	424	342
1518	212	234	242	256	267	298	280
1522	215	233	240	267	284	328	277
1528	253	267	273	298	299	361	277
1529	245	254	269	278	292	355	256
1602	258	284	300	312	333	398	321
1606	252	263	266	272	296	369	280
1610	248	270	281	293	327	393	298
1614	231	254	261	264	284	344	268
1618	252	274	287	297	322	383	290
1622	236	272	284	302	333	393	300
1626	244	269	272	285	294	352	289
1630	218	252	266	283	314	385	295
1634	212	228	234	248	272	322	247
1638	214	231	237	255	277	329	257
1642	228	242	249	273	295	364	275
1646	213	220	235	250	275	241	253

APPENDIX F

INDIVIDUAL MATERNAL BODY WEIGHTS-GRAMS
(Pregnant Rats Only)
TRINITRO-ROX
6 mg/kg/day

Dam Number	Day 0 Mated	Day 6 Treatment Starts	Day of Gestation Day 10	Day 13	Day 16 Post-Treatment	Day 20 Sacrifice	Day 20 Adjusted
1437	223	246	257	247	267	332	257
1467	239	259	267	270	298	338	273
1468	214	239	243	257	276	344	265
1471	197	214	223	245	267	306	228
1474	213	230	232	249	251	279	253
1475	212	236	241	258	270	318	267
1476	190	208	213	231	257	320	243
1479	270	286	301	318	349	424	321
1482	197	219	231	242	261	319	242
1483	210	227	234	254	273	340	264
1484	220	239	240	244	227	260	250
1485	237	255	262	274	302	346	270
1486	236	244	254	269	286	339	262
1487	234	248	258	268	273	340	244
1488	282	292	284	314	333	370	302
1489	219	243	253	277	279	336	262
1490	231	249	264	283	301	367	271
1491	250	273	285	289	318	376	283
1523	199	215	219	227	242	267	234
1603	251	281	285	301	318	387	303
1607	243	274	272	287	303	373	287
1615	248	271	283	292	330	406	302
1619	215	231	236	241	268	324	237
1623	233	260	268	271	306	364	270
1627	235	254	245	256	277	327	268
1631	225	240	233	244	270	336	257
1639	227	245	246	252	282	343	270
1643	239	266	260	281	303	368	285
1647	200	220	221	242	258	308	235

APPENDIX G

INDIVIDUAL MATERNAL BODY WEIGHTS-GRAMS
(Pregnant Rats Only)
TRINITRO-RDX
20 mg/kg/day

Dam Number	Day 0 Mated	Day 6 Treatment Starts	Day 10	Day 13	Day 16 Post-Treatment	Day 20 Sacrifice	Day 20 Adjusted
				Day of Gestation			
1492	230	248	249	236	247	304	244
1496	196	184	221	223	229	279	242
1497	201	220	212	204	223	288	213
1500	221	245	236	242	265	341	257
1505	218	239	225	232	256	339	260
1507	208	216	199	205	272	275	235
1508	196	205	177	187	210	256	209
1512	247	254	246	273	305	376	301
1513	236	248	235	255	262	300	232
1524	229	256	245	258	292	366	276
1527	233	246	224	249	265	331	256
1608	257	273	249	267	308	390	280
1624	233	257	228	242	262	340	258
1628	248	264	238	255	276	351	266
1640	223	238	224	239	262	316	254
1644	228	239	229	254	275	344	260
1648	203	230	211	236	265	326	250
1653	270	295	264	238	281	346	275
1654	258	263	248	283	298	374	295
1656	250	265	236	267	286	366	276
1657	234	264	267	292	308	399	291
1658	240	255	254	278	295	380	292
1659	233	250	246	265	276	340	273
1668	249	248	242	277	292	339	260
1669	253	275	263	284	270	304	230

APPENDIX H

INDIVIDUAL LITTER DATA
GUM ACACIA CONTROLS

Dam No.	Corpora Lutea	Implantation Sites	Early Resorptions	Late Resorptions	Total Resorptions	Live Fetuses	Dead Fetuses	Total Fetuses	Average Fetal Weight (gm)	Average Fetal Length (cm)	Fetuses Malformed Fetuses with Variations	Sex M/F
1417	11	8	2	0	2	6	0	6	4.81	4.0	0/0	2/4
1419	16	5	0	0	0	5	0	5	3.62	3.4	1/0	1/4
1422	14	12	1	0	1	11	0	11	4.28	4.0	0/0	7/4
1426	14	14	1	0	1	13	0	13	3.56	3.6	0/2	7/6
1428	22	15	1	0	1	14	0	14	3.56	3.6	0/0	8/6
1430	17	15	0	0	0	15	0	15	3.69	3.7	0/2	7/8
1434	14	8	0	0	0	8	0	8	3.63	3.8	0/1	2/6
1435	15	14	0	0	0	14	0	14	3.46	3.7	0/0	3/11
1436	25	17	0	0	0	17	0	17	2.86	3.4	0/9	6/11
1439	15	15	1	0	1	14	0	14	3.61	3.7	0/0	6/8
1441	19	16	0	0	0	16	0	16	5.06	4.0	0/0	6/10
1521	17	16	0	0	0	16	0	16	3.75	3.8	0/1	10/6
1601	17	17	1	0	1	16	0	16	3.58	3.6	0/1	11/5
1605	20	17	2	0	2	15	0	15	3.93	3.8	1/0	6/9
1609	17	17	0	0	0	17	0	17	3.41	3.6	0/0	9/8
1613	17	14	0	0	0	14	0	14	3.98	3.7	0/0	5/9
1617	16	15	1	0	1	14	0	14	4.40	3.9	0/1	8/6
1621	16	15	0	0	0	15	0	15	4.32	3.8	0/0	7/8
1625	16	15	1	0	1	14	0	14	3.92	3.7	0/3	7/7
1629	18	16	0	0	0	16	0	16	3.45	3.6	0/0	7/9
1633	16	12	1	0	1	11	0	11	3.90	3.9	0/3	4/7
1637	22	13	2	0	2	11	0	11	3.65	3.6	0/0	6/5
1641	16	15	0	0	0	15	0	15	3.74	3.7	0/0	5/10
1645	17	16	3	0	3	13	0	13	3.68	3.6	0/0	3/10
1649	15	15	0	0	0	15	0	15	3.34	3.6	0/0	9/6

APPENDIX I

INDIVIDUAL LITTER DATA
ROX, 2 mg/kg/DAY

Dam No.	Corpora Lutea	Implantation Sites	Early Resorptions	Late Resorptions	Total Resorptions	Live Fetuses	Dead Fetuses	Total Fetuses	Average Fetal Weight (gm)	Average Fetal Length (cm)	Fetuses Malformed Fetuses with Variations	Sex M/F
1444	20	16	0	0	0	16	0	16	3.68	3.7	0/0	7/9
1446	15	15	0	0	0	15	0	15	3.89	3.7	0/0	5/10
1454	20	14	1	0	1	13	0	13	3.55	3.6	0/3	5/8
1459	19	16	1	0	1	15	0	15	3.64	3.7	0/0	4/11
1460	5	5	0	0	0	5	0	5	4.02	3.9	0/0	3/2
1461	16	14	0	0	0	14	0	14	3.55	3.7	0/3	3/11
1463	16	15	1	0	1	14	0	14	3.91	3.6	0/2	13/1
1464	19	18	1	0	1	17	0	17	3.47	3.6	0/0	5/12
1465	17	17	3	0	3	14	0	14	3.74	3.8	0/0	6/8
1518	12	2	0	0	0	2	0	2	5.14	4.3	0/0	1/1
1522	14	10	1	0	1	9	0	9	3.44	3.6	0/0	4/5
1528	19	17	1	0	1	16	0	16	3.40	3.6	0/2	9/7
1529	15	15	1	0	1	14	0	14	3.76	3.8	0/0	8/6
1602	22	17	3	0	3	14	0	14	3.60	3.7	0/0	8/6
1606	20	16	1	0	1	15	0	15	3.93	3.8	0/0	7/8
1610	17	17	1	0	1	16	0	16	3.79	3.7	0/1	9/7
1614	15	14	1	0	1	13	0	13	3.70	3.7	0/0	6/7
1618	16	15	0	0	0	15	0	15	4.31	3.6	0/3	6/9
1622	17	17	1	0	1	15	1	16	3.79	3.7	0/1	4/12
1626	15	14	2	0	2	12	0	12	3.31	3.5	0/0	4/8
1630	15	15	0	0	0	15	0	15	3.70	3.6	0/2	11/4
1634	14	14	0	0	0	14	0	14	3.26	3.5	0/1	9/5
1638	15	15	2	0	2	13	0	13	3.61	3.6	0/2	7/6
1642	18	18	1	0	1	17	0	17	3.31	3.5	0/0	9/8
1646	18	17	0	0	0	17	0	17	3.38	3.5	1/2	7/10

APPENDIX J

INDIVIDUAL LITTER DATA
RDX, 6 mg/kg/DAY

Dam No.	Corpora Lutea	Implantation Sites	Early Resorptions	Late Resorptions	Total Resorptions	Live Fetuses	Dead Fetuses	Total Fetuses	Average Fetal Weight (gm)	Average Fetal Length (cm)	Fetuses Malformed Fetuses with Variations	Sex M/F
1437	14	13	0	0	0	13	0	13	3.60	3.7	0/0	5/8
1467	16	11	2	0	2	9	0	9	4.84	4.1	0/1	3/6
1468	17	15	2	0	2	13	0	13	3.64	3.7	0/0	7/6
1471	15	14	0	0	0	14	0	14	3.62	3.7	0/3	5/9
1474	10	4	0	0	0	4	0	4	3.38	3.6	0/0	1/3
1475	16	9	0	0	0	9	0	9	3.48	3.6	0/1	5/4
1476	17	13	0	0	0	13	0	13	3.77	3.7	0/3	7/6
1479	21	18	1	0	1	17	0	17	3.64	3.7	0/0	5/12
1482	18	14	0	0	0	14	0	14	3.61	3.6	0/1	6/8
1483	16	16	3	0	3	13	0	13	3.50	3.6	0/0	4/9
1484	11	2	1	0	1	1	0	1	4.22	4.0	0/0	0/1
1485	18	15	1	0	1	14	0	14	3.72	3.8	0/0	7/7
1486	15	15	3	0	3	12	0	12	3.50	3.6	0/1	6/6
1487	18	17	0	0	0	17	0	17	3.86	3.6	0/0	7/10
1488	19	10	0	0	0	10	0	10	3.81	3.8	0/1	4/6
1489	17	13	3	0	3	10	0	10	3.82	3.8	0/2	6/4
1490	16	15	0	0	0	15	0	15	4.29	3.6	0/2	10/5
1491	18	18	0	0	0	18	0	18	3.57	3.4	0/1	8/10
1523	18	5	0	0	0	5	0	5	3.72	3.8	0/1	2/3
1603	20	16	1	0	1	15	0	15	3.55	3.6	0/0	10/5
1607	16	16	1	0	1	15	0	15	3.88	3.8	0/0	7/8
1615	21	17	0	0	0	17	0	17	3.79	3.6	0/2	10/7
1619	18	15	0	0	0	15	0	15	3.86	3.7	0/0	7/8
1623	17	17	0	0	0	17	0	17	3.78	3.6	0/1	8/9
1627	20	15	3	0	3	12	0	12	2.85	3.4	0/1	4/8
1631	17	16	0	0	0	16	0	16	3.25	3.5	0/1	10/6
1639	16	15	2	0	2	13	0	13	3.73	3.6	0/1	7/6
1643	14	14	0	0	0	14	0	14	3.80	3.6	0/1	12/2
1647	15	13	0	0	0	13	0	13	3.76	3.6	0/1	6/7

APPENDIX K

INDIVIDUAL LITTER DATA
RDX, 20 mg/kg/DAY

Dam No.	Corpora Lutea	Implantation Sites	Early Resorptions	Late Resorptions	Total Resorptions	Live Fetuses	Dead Fetuses	Total Fetuses	Average Fetal Weight (gm)	Average Fetal Length (cm)	Fetuses Malformed Fetuses with Variations	Sex M/F
1492	11	11	2	0	2	9	0	9	4.78	4.1	0/2	5/4
1493	1	1	1	0	1	0	0	0	NA	NA	NA	NA
1496	17	7	0	0	0	7	0	7	3.04	3.3	0/1	5/2
1497	16	14	0	0	0	14	0	14	3.59	3.7	0/1	5/9
1500	17	16	0	0	0	16	0	16	3.12	3.4	0/0	7/9
1505	18	15	2	0	2	13	0	13	3.77	3.8	0/1	10/3
1507	14	10	3	0	3	7	0	7	3.65	3.7	0/1	6/1
1508	17	14	2	1	3	11	0	11	2.45	3.2	1/1	5/6
1512	14	14	0	0	0	14	0	14	3.44	3.6	0/3	5/9
1513	15	14	0	0	0	14	0	14	3.37	3.2	0/2	8/6
1524	24	17	0	0	0	17	0	17	3.54	3.7	0/4	7/10
1527	15	15	2	0	2	13	0	13	3.70	3.4	0/1	4/9
1608	23	20	1	0	1	19	0	19	3.47	3.7	0/0	12/7
1624	19	17	2	0	2	15	0	15	3.34	3.5	1/1	8/7
1628	22	17	1	0	1	16	0	16	3.37	3.5	0/2	9/7
1640	19	13	2	0	2	11	0	11	3.59	3.5	0/1	3/8
1644	16	16	1	0	1	15	0	15	3.60	3.6	0/2	6/9
1648	19	15	0	0	0	15	0	15	3.26	3.5	0/0	9/6
1653	18	16	1	0	1	15	0	15	2.85	3.6	0/3	6/9
1654	18	14	0	0	0	14	0	14	3.50	3.3	0/0	5/9
1656	17	17	1	0	1	16	0	16	3.68	3.4	0/1	7/9
1657	18	18	0	0	0	18	0	18	4.04	3.8	0/0	10/8
1658	17	17	1	0	1	16	0	16	3.41	3.5	0/1	8/8
1659	14	14	0	0	0	14	0	14	2.99	3.2	0/0	4/10
1668	15	15	0	0	0	15	0	15	3.50	3.5	0/3	9/6
1669	19	16	1	0	1	15	0	15	3.13	3.4	0/1	11/4

Study No. 75-51-0573-86, Jun 85 - Jan 86

APPENDIX L

ANALYTICAL QUALITY ASSURANCE

The Analytical Quality Assurance Office certifies the following:

a. This study was conducted in accordance with:

(1) Standing Operating Procedures developed by the Toxicology Division, USAEHA.

(2) Title 40, Code of Federal Regulations, Part 160, Pesticide Programs: Good Laboratory Practice Standards, 2 May 1984.

b. Facilities were inspected during the study operations phases to ensure compliance with paragraph a, above.

c. The information presented in this report accurately reflects the new data generated during the course of conducting this study.

PAUL V. SNEERINGER, Ph.D.
Chief, Analytical Quality
Assurance Office

APPENDIX M
RDX ANALYSIS

DESCRIPTION SHEET FOR EXPLOSIVES, CHEMICALS, ETC. (DRSAR-P-702-109)	RQR CONTROL SYMBOL EXEMPT PARA. 7-2A AR 335-15	PAGE 1 OF 1

TO:	FROM:	DATE:
COMMANDER US ARMY ARMAMENT MATERIAL READINESS COMMAND ATTN: DRSAR-QAD ROCK ISLAND, IL 61201	COMMANDER HOLSTON ARMY AMMUNITION PLANT KINGSPORT, TENN. 37660	July 15, 1985 MATERIAL: Washed Crude RDX

MANUFACTURER	CONTRACT NO.
HOLSTON DEFENSE CORPORATION	DAAA09-83-C-4515

SECTION A - DESCRIPTION OF LOTS

FROM NUMBER	THRU NUMBER	TOTAL NO. LOTS	TOTAL NET AMOUNT ACCEPTED
N/A	N/A	N/A	200 Grams

PLACE MANUFACTURED	SPECIFICATION AND AMENDMENT/DRAWING NO.
KINGSPORT, TENNESSEE	Shipping Order AMCCOM-1[illegible]08-85

SECTION B - DESCRIPTION OF MATERIAL

March 4, 1986

Batch No. 332RW-2639 200 Grams

Mr. Rich Angerhofer
Toxicology Division
USAEHA
Building E-2100
Aberdeen Proving Ground, MD 21010

Nominal Values:

% RDX	% HMX (Beta Polymorph)	% Acetic Acid	Median Particle Diameter
90	10	0.3	40 Micron

REMARKS CLIN 0010AC
Washed crude RDX from the E-building

SECTION C - CERTIFICATION

SAMPLING CONDUCTED BY CONTRACTOR	THE ABOVE MATERIAL COMPLIES WITH ALL SPECIFICATION REQUIREMENTS AND IS CERTIFIED TRUE AND CORRECT.
TESTING CONDUCTED BY CONTRACTOR	July 15, 1985 DATE — C. W. Crane SIGNATURE

THE ABOVE DESCRIBED LOTS ARE HEREBY ACCEPTED — 21730 — FOR THE COMMANDER

16 July 85 DATE — Chief, Quality Assurance Div — for James E. Curtis SIGNATURE

ARRCOM FORM 213-R, FACSIMILE

END

FILMED

5-86

DTIC